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The hippocampal network model: A transdiagnostic metaconnectomic approach

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ABSTRACT

Purpose: The hippocampus plays a central role in cognitive and affective processes and is commonly implicated in neurodegenerative diseases. Our study aimed to identify and describe a hippocampal network model (HNM) using trans-diagnostic MRI data from the BrainMap® database. We used meta-analysis to test the network degeneration hypothesis (NDH) (Seeley et al., 2009) by identifying structural and functional covariance in this hippocampal network.

Methods: To generate our network model, we used BrainMap's VBM database to perform a region-to-whole-brain (RtWB) meta-analysis of 269 VBM experiments from 165 published studies across a range of 38 psychiatric and neurological diseases reporting hippocampal gray matter density alterations. This step identified 11 significant gray matter foci, or nodes. We subsequently used meta-analytic connectivity modeling (MACM) to define edges of structural covariance between nodes from VBM data as well as functional covariance using the functional task-activation database, also from BrainMap. Finally, we applied a correlation analysis using Pearson's r to assess the similarities and differences between the structural and functional covariance models.

Key findings: Our hippocampal RtWB meta-analysis reported consistent and significant structural covariance in 11 key regions. The subsequent structural and functional MACMs showed a strong correlation between HNM nodes with a significant structural-functional covariance correlation of $r = .377$ ($p = .000049$).

Significance: This novel method of studying network covariance using VBM and functional meta-analytic techniques allows for the identification of generalizable patterns of functional and structural abnormalities pertaining to the hippocampus. In accordance with the NDH, this framework could have major implications in studying and predicting spatial disease patterns using network-based assays.

1. Introduction

The hippocampus is arguably the most well studied sub-cortical region in both humans and animals due in large part to its functional role in the cognition of learning and memory. When compromised, symptoms of hippocampal dysfunction are distinguished by impairments in memory, attention, emotion, spatial navigation, and executive function. Pathologically, hippocampal disease is characterized by neuronal degeneration progressing to structural atrophy detectable by magnetic resonance imaging (MRI), as in the cases of Alzheimer's disease (AD) (Schröder and Pantel, 2016), mild cognitive impairment (MCI) (Huijbers et al., 2015), mesial temporal lobe epilepsy (MTLE) (Mumoli et al., 2013), and schizophrenia (Radulescu et al., 2014). In terms of network topology, the hippocampus has been characterized as a hub, exhibiting structural covariance with multiple other brain regions, in keeping with its central role in multiple cognitive processes. It has been suggested that metabolic demands of hubs make such structures selectively vulnerable to neuropsychiatric diseases (Goodkind et al., 2015; Crossley et al., 2014), arguing for converging structural and functional network abnormalities. Advances in resting state functional MRI (fMRI) and sophisticated meta-analytic methodologies have allowed researchers to exhaustively map and quantify functional covariance networks (Fox and Raichle, 2007; Smith et al., 2009; Crossley et al., 2013). Nevertheless, our understanding of the relationships

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between functional and structural networks in the human brain, as can be studied using MRI, remains in its infancy. In 2009, Seeley et al., postulated the "network degeneration hypothesis" (NDH), which predicts that disease atrophy patterns should recapitulate healthy functional network architecture with recent studies beginning to address this question in the context of disease-specific network changes (Lefort-Besnard et al., 2018). Our aim in this study was to test the NDH meta-analytically and trans-diagnostically using the hippocampus as the central hub, thereby creating a hippocampal network model (HNM) that should be applicable in multiple neuropsychiatric and systemic disorders.

Structural and functional connectivity are two procedurally distinct, but conceptually linked constructs, both exhibiting network properties. Functional connectivity networks can be extracted by functional covariances, either at rest or during task performance, and exhibit interconnected sets of brain regions that interact to perform specific perceptual, motor, cognitive, and affective functions (Bressler and Menon, 2010). Structural covariance networks are inferred from inter-regional morphometric covariances across subjects (e.g. gray matter atrophy, cortical thinning). The notion that structural covariance is fundamental to functional network connectivity is based on the expectation that functional processes can exert trophic influences that, over time, modify gray matter volume enough to be detected as structural covariance patterns (Seeley et al., 2009; Gong et al., 2012). Multiple competing and converging hypotheses have been put forward to explain disease-related structural covariance, these include: 1) transneuronal spread, 2) nodal stress, 3) trophic failure, and 4) shared vulnerability (Zhou et al., 2012). For this reason, structural covariance has been extensively studied in the characterization of neurocognitive development (Alexander-Bloch et al., 2013; Lerch et al., 2006), aging (Marstaller et al., 2015; Montembeault et al., 2016), and in neurodegenerative disorders (Seeley et al., 2009; Spreng and Turner, 2013). The NDH suggests a close relationship between structure and function whereby abnormalities in structural covariance, functional covariance and behavior will be mutually predictive in brain disorders.

Meta-analytic computation of functional covariance is well-established (Smith et al., 2013; Crossley et al., 2013). In assessing functional connectivity networks, activation likelihood estimation (ALE) is an extensively validated technique used in meta-analyses that pools 3D coordinates in stereotactic space from a number of like studies applied to functional task-activation studies (Laird et al., 2005; Turkeltaub et al., 2011). It achieves this by analyzing voxel-wise, univariate effects across experiments and generates a probability distribution centered at the respective coordinates. A natural extension of ALE, meta-analytic connectivity modeling (MACM) is a study-wise multivariate approach used to generate functional covariance networks from activation patterns reported across a range of experimental neuroimaging tasks and paradigms (Laird et al., 2009a; Robinson et al., 2010; Eickhoff et al., 2010a). In MACM, an ALE score is generated for every voxel, which are then converted into p values to identify areas of significance with scores higher than empirically-derived null distributions (Turkeltaub et al., 2011; Laird et al., 2005; Eickhoff et al., 2012). This technique has been found to correspond well with numerous mathematical computational formalisms including seed-based resting state (Jiang et al., 2015), independent components analyses (Smith et al., 2009), and graph theory (Crossley et al., 2013). Although MACM and ALE have been validated and replicated considerably in functional studies and, recently, using structural data (Langner et al., 2014; Reid et al., 2016), the present study aims to adopt these methods for investigating structural covariance using a meta-analytical and trans-diagnostic approach with VBM.

Voxel-based morphometry (VBM) is a widely-used technique to identify subtle, disease-related structural changes that cannot be easily observed on visual analysis. VBM achieves this by standard space brain registration and group-averaging, comparing gray matter densities between patients and controls, producing disease-specific atrophy patterns computed in a univariate, voxel-wise manner. VBM studies have reported regional gray matter atrophy and hypertrophy patterns in thousands of peer-reviewed publications spanning over one hundred diseases. Indeed, VBM studies constitute a large body of quantitative literature reporting a vast number of areas of focal structural change in the brain (Ashburner and Friston, 2000). Coordinate-based reporting and whole-brain coverage are sine qua non for meta-analysis; VBM meets both criteria. Using VBM, then, meta-analytic methods 1) can compute convergent patterns of atrophy and hypertrophy in a cross-study manner; 2) can compute structural covariance network, using between-study, co-atrophy patterns. The multiple reports of VBM studies conducted within diseases and across diseases using a standardized coordinate space makes it well suited for coordinate-based meta-analytic structural covariance analyses studies (Glahn et al., 2008; Fox et al., 2014; Crossley et al., 2015).

A transdiagnostic approach, as opposed to disease-specific, for studying structural covariance networks can most readily be achieved through meta-analysis. In recent years, a growing literature of transdiagnostic neuroimaging has been used in the meta-analytic investigation of neuropsychiatric pathology. Numerous reports indicate that diseases of the brain tend to exhibit patterns of convergence, both structurally and functionally (Seeley et al., 2009; Crossley et al., 2013; Goodkind et al., 2015; McTeague et al., 2016). This new approach – grouping studies by neurobiological effects rather than by diagnostic category – corresponds closely to the Research Domain Criteria (RDoC) initiative set forth in 2010 to "create a new kind of taxonomy for mental disorders by bringing the power of modern research and approaches in genetics, neuroscience, and behavioral science to the problems of mental illness." (Insel et al., 2010). Clinical and neurobiological data has also suggested that psychiatric disorders are more comorbid than previously thought. They share common imaging and genetic markers, and demonstrate alterations across neural networks that mediate cognition and other mental processes (Etkin and Cuthbert, 2014). Moreover, there is much interest and support within the neuroscience community in leveraging large brain imaging databases for the purpose gaining deeper insight into neuroscientific phenomena (Crossley et al., 2016; Bzdok and Yeo, 2017).

BrainMap (Fox et al., 1994; Fox and Lancaster, 2002) is a neuroimaging database of published neuroimaging experiments with coordinate-based results in standard space. Its collection of functional task-based activation and structural gray matter atrophy enables investigators to study human brain function and structure in healthy and disease subjects meta-analytically. Its functional database currently contains 3197 functional publications spanning over one hundred paradigms with 15,834 experiments and 69,727 subjects. Additionally, the VBM database contains 993 publications spanning over one hundred diseases with 3150 experiments and 75,709 subjects (Laird et al., 2012; Laird et al., 2009b). In our study, we utilized MACM, a study-wise multivariate method to assess covariance across structural networks using BrianMap's VBM transdiagnostic literature (Eickhoff et al., 2010b). Previously, MACM has been used to investigate functional covariance between brain regions that are functionally connected across task-activation experiments (Fox et al., 2005a; Robinson et al., 2010; Laird et al., 2013). To our knowledge this paper is the first to employ MACM to generate a structural covariance model using BrainMap's transdiagnostic VBM database. In our endeavor to test the NDH, we believe that using the MACM method is well suited to investigate anatomic/activation likelihood estimate correlations found between structural and functional covariance models.

In this study, we computed a structural covariance model of the hippocampus – the HNM – beginning with a region-to-whole brain trans-diagnostic VBM meta-analysis (also known as a single-seed MACM analysis). We identified 11 significant nodes using a rigorous voxel-level family-wise error (FWE) of 0.01. These 11 nodes of interest were then re-seeded into the BrainMap database as standardized spherical ROIs to generate two MACM models: 1) structural covariance (significant regions of gray matter density changes), from the VBM